NIH MSM Abstract

# A Multi-scale systems pharmacology approach to tuberculosis therapy

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Designing successful drug regimens to treat disease can be difficult. Positive results from preclinical and *in vitro* experiments do not necessarily translate to clinical efficacy, resulting in failed clinical trials. Tuberculosis (TB), caused by the pathogen *Mycobacterium tuberculosis*, is treated with combinations of antibiotics to limit the development of resistance, so designing the best combination and dosing schedule is a complex problem. One pathological characteristic of TB is the formation of lesions called granulomas. These granulomas further complicate regimen design by introducing a physiological environment that harbors subpopulations of bacteria that are phenotypically tolerant to certain antibiotics and also limits antibiotic distribution. Rational design of new antibiotic regimens to treat TB requires an understanding of drug distribution in these granulomas, as well as the bactericidal activity of different antibiotics.

We designed an integrated computational and experimental approach to optimizing drug regimens for TB. We developed a multi-scale computational model to simulate granuloma formation, antibiotic distribution and antibiotic treatment. We utilize a cellular and tissue scale agent-based model to simulate immune cell and bacterial interactions on a two- or three-dimensional spatial grid to capture the emergent behavior of granuloma formation.. At the molecular scale, blood vessels in the agent-based model deliver antibiotics onto the grid (lung tissue) where the antibiotics undergo diffusion, extracellular binding, and cellular partitioning. A pharmacodynamics model estimates the concentration-dependent killing rate constant and the probability a given bacterium will be killed during treatment simulation. Calibrating the pharmacokinetics and pharmacodynamics of different antibiotics based on experimental data allows us to simulate treatment with a regimen of any combination of antibiotics. However, the 'regimen design space' for possible combinations of antibiotics is still too large to search exhaustively even using computation. We apply a surrogate-assisted optimization framework to predict which combinations of antibiotics and dosing schedules produce optimal sterilizing regimens, providing an efficient way to identify optimal regimens. Ultimately, this computational framework provides a pipeline to predict regimen efficacy on a sample of virtual patients through a virtual clinical trial. Using a computational framework to predict optimal drug regimens can aid in the rational design of regimens with higher success rates.